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Wegener's granulomatosis and the heart

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Abstract

Three cases of Wegener's granulomatosis with cardiac complications are described and the relevant published reports are reviewed. The first case of Wegener's granulomatosis was associated with aortic regurgitation and required aortic valve replacement. The second and third cases were associated with pericardial disease requiring pericardiectomy for constructive pericarditis in one case, and haemorrhagic pericarditis with pericardial effusion in the other. Aortic valve involvement in Wegener's granulomatosis is uncommon and valve replacement has been described on only one previous occasion. Pericardial involvement is relatively common pathologically, but pericardial surgery has been described in this condition only twice, once for tamponade and once for constrictive pericarditis after pericardiocentesis. Cardiac involvement is not uncommon in patients with Wegner's granulomatosis and may be clinically important. Diagnosis is aided by estimation of the anti-neutophil cytoplasmic antibody titre.

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Wegener's granulomatosis is an uncommon disease characterised by a necrotising granulomatous vasculitis affecting the upper and lower respiratory tract and the kidneys. Cardiac involvement has been reported in 6%–44% of cases.[1 2]

Case reports

CASE 1

A 32 year old man was referred in December 1990 for investigation of aortic regurgitation. He had had a nephrectomy in childhood. A heart murmur had been noted in 1986, at the time of an undocumented illness during which he lost half of his teeth. In 1989 he developed nasal crusting, deafness, arthritis, a rash, red eyes, malaise, and fever. A classic anti-neutrophil cytoplasmic antibody (c-ANCA) test was positive and a diagnosis of Wegener's granulomatosis was made. Treatment with cyclophosphamide and corticosteriods was started, with rapid improvement in his symptoms. No abnormality of renal function or on chest radiographs was found at any stage.

At the time of referral he had a 12 month history of dyspnoea on exertion but was otherwise well. Medication comprised 150 mg cyclophosphamide on three days each week and 2·5 mg prednisolone daily. On examination his blood pressure was 150/30 mm Hg and the arterial pulse was collapsing in character. On auscultation aortic systolic and diastolic murmurs, a fourth heart sound, and an Austin Flint murmur were heard. An electrocardiogram showed first degree atrioventricular block (PR interval 300 ms) and voltage criteria of left ventricular hypertrophy (fig 1). His chest *x* ray film showed car-

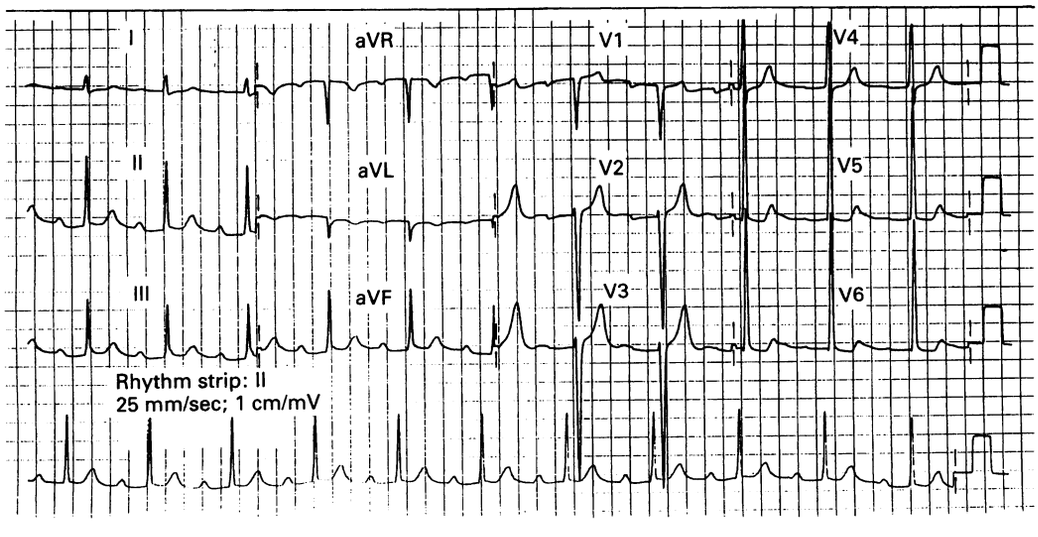

Figure 1 Twelve lead ECG from case 1 showing left ventricular hypertrophy and first degree atrioventricular block.

diomegaly and some upper lobe venous engorgement. Echocardiography showed a severely dilated left ventricle with a diastolic short axis diameter of 7·4 cm. The ejection fraction was estimated at 55%. Doppler examination showed aortic and mitral regurgitation. The ascending aorta was dilated (4·5 cm).

Cardiac catheterisation confirmed these findings, showing severe aortic regurgitation and mild generalised ventricular dysfunction (ejection fraction 45%). The left ventricular end diastolic pressure was 18 mm Hg. Coronary angiography was normal.

His c-ANCA titre was raised at 1:300 (normal less than 1:30), similar to previous measurements since remission of his Wegener's granulomatosis; other variables were haemoglobin, 11·7 g/dl; platelets, 155 × 10^9; urea, 8·4 mmol/l; creatinine, 0·11 mmol/l; and C-reactive protein, 0·3 mg/dl. Quiescent limited Wegener's granulomatosis associated with aortic regurgitation was diagnosed.

Aortic valve replacement with a 29 mm Medtronic Hall prosthesis was performed on 16 August 1991 without complications and he has subsequently been free from cardiac symptoms. At operation, the aortic root was dilated with apparently normal cusps failing to meet centrally. There were mild pericardial adhesions. Valve histology showed a tricuspid aortic valve with myxoid degeneration, focal fibrosis, and neovascularisation. No granulomata, inflammatory cells, or Aschoff bodies were seen.

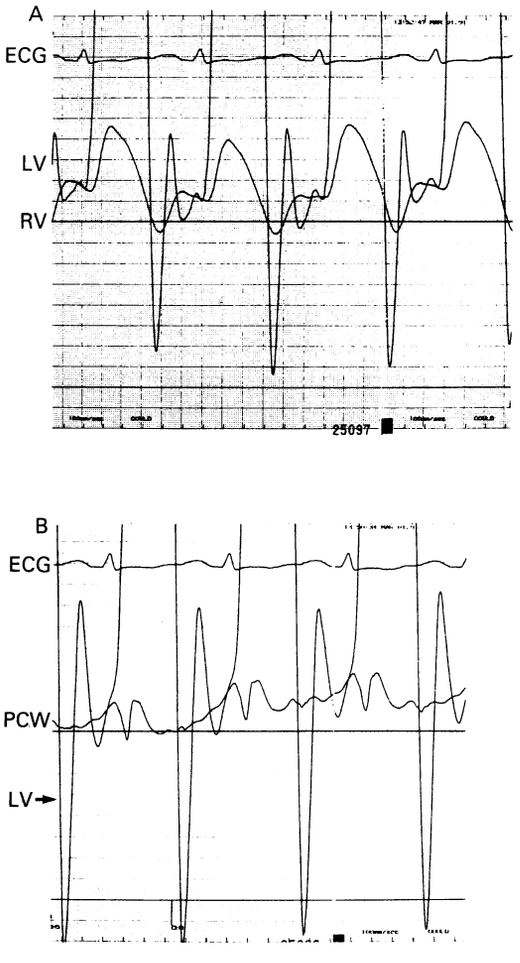

Figure 2 (A) Simultaneous right (RV) and left (LV) ventricular pressure traces: (B) simultaneous LV and pulmonary capillary wedge pressure (PCW) traces (calibration lines at 20 mm Hg). Both show equalisation of intracardiac pressures, together with the dip and plateau left ventricular waveform typical of constrictive pericarditis.

CASE 2

A 45 year old man presented with refractory cardiac failure in February 1992. Wegener's granulomatosis had been diagnosed in 1971 on the basis of lung cavitations and a rash that was biopsied and showed granulomatous disease. He was treated with cyclophosphamide and prednisolone for eight years after which treatment was gradually withdrawn. In 1987 he had developed progressive fibrosis of the quadriceps muscles of both legs that caused pain in the thighs and restriction of knee movement (0–40°). Open quadriceps biopsy showed extensive fibrosis including areas of young fibroblasts and mature collagen fibres, focal neovascularisation, and a lymphocytic infiltrate were present. For two years previously he had had recurrent sinusitis and haemoptysis. Three months before presentation, he was diagnosed as having cardiac failure that initially responded to medical treatment.

On examination he had engorged neck veins, gross peripheral oedema, hepatomegaly, ascites, and basal crackles in the lung fields. There was fibrosis of the quadriceps bilaterally and leg lesions compatible with stasis ulceration. Otorhinological examination showed nasal crusting but no ulceration.

The electrocardiogram showed widespread non-specific T wave and ST segment changes; the chest *x* ray film was normal and there was no pericardial calcification. Echocardiography showed a small vigorous left ventricle. No pericardial fluid or abnormality of the pericardium were seen. The right side of the heart and valves were normal. Abdominal ultrasound showed gross ascites but no other abnormality. A presumptive diagnosis of constrictive pericarditis was made.

Left ventriculography showed mild apical hypokinesia with an ejection fraction of 55%. The coronary arteries had diastolic pinching consistent with constrictive pericarditis but were angiographically normal. Pressure measurements showed equalisation of the diastolic pressures within the heart with right and left ventricular end diastolic pressures of 18 mm Hg, mean pulmonary capillary wedge pressure of 22 mm Hg, and mean right atrial pressure of 23 mm Hg (fig 2 A and B). Right ventricular biopsy was normal with no granulomata or amyloid.

His c-ANCA titre was positive at 1:1000 and his haemoglobin was reduced at 10·9 g/dl with a microcytic picture. Other values were platelets, 202 × 10^9/l; erythrocyte sedimentation rate, 22 mm/h; creatinine, 0·08 mmol/l; and alkaline phosphatase, 114 IU/l. Immunoglobulins were slightly raised (IgG 18·3 g/l, IgA 4·5 g/l), rheumatoid factor positive (sheep cell agglutination test, 128 IU), and the anti-nuclear factor was negative.

A diagnosis of Wegner's granulomatosis and of constrictive pericarditis was made.

The Wegner's granulomatosis was considered to be in only partial remission, on the basis of the nasal features (and possibly the leg ulceration) together with the c-ANCA titre. The patient was treated with cyclophosphamide (0·4 mg/m^2) once monthly for three months (together with mesna), and prednisolone (20 mg) daily, with the intention of controlling the activity of the disease before cardiac surgery.

Three months later his nasal symptoms had improved with a reduction in his c-ANCA titre to 1:100 and he underwent pericardiectomy without complications. At operation, the pericardium was found to be grossly thickened and histology showed fibrosis with few blood vessels. No evidence of granulomata or active vasculitis was seen.

Subsequently he has improved with a substantial reduction in his diuretic requirement.

CASE 3

A 35 year old woman was referred with a pericardial effusion for consideration of surgery in January 1991.

Wegener's granulomatosis had been diagnosed in 1985 when she presented with loss of weight of three stone, dermal vasculitis, arthritis, episcleritis, sinusitis with bloody nasal discharge, and rapidly declining renal function. Renal biopsy showed a necrotising crescentic glomerulonephritis. After treatment with daily oral cyclophosphamide plasma creatinine fell from a peak of 0·89 mmol/l to just over 0·2 mmol/l. After one year treatment was changed to azathioprine. Renal function began to decline slowly despite reintroduction of cyclophosphamide. This was stopped in July 1990 because of persistent leucopenia and thrombocytopenia, when plasma creatinine was 0·78 mmol/l.

In August and September 1991 she had a florid exacerbation of her Wegener's granulomatosis with a series of life threatening lung haemorrhages. Her c-ANCA titre, which had previously been mildly positive at 1:30 was higher at 1:100. She had a series of improvements and relapses, responding to stepwise increases in immunosuppression with cyclophosphamide, high doses of prednisolone, repeated courses of plasma exchange, intravenous immunoglobulin, and the monoclonal antibody OKT3. During this illness she also required blood and platelet transfusions and her renal function further declined requiring regular haemodialysis.

She recovered steadily from this illness and was very well for a few months until December 1991 when she experienced chest pain and increasing shortness of breath. At the time of referral, her immunosuppressive medication consisted of monthly intravenous cyclophosphamide (0·25 g/m^2) and oral prednisolone (15 mg) daily.

On examination she was pale with a puffy face and ankle swelling. An arteriovenous fistula was present in the left upper arm. Her blood pressure was 140/80 mm Hg. Examination of the heart and chest was normal.

Investigation showed haemoglobin, 5·7 g/dl; platelets 124 × 10^9; urea, 16·5 mmol/l; creatinine, 0·65 mmol/l; and a negative c-ANCA titre. Biochemistry was otherwise normal. A chest *x* ray film showed a large heart but was otherwise unremarkable. Echocardiography showed a moderately large pericardial effusion, with abnormal right atrial movement suggesting haemodynamic importance, the left ventricle was small and vigorous with an estimated ejection fraction of 60%, there was mild mitral regurgitation on Doppler examination.

The patient underwent pericardial fenestration in January 1992, and received a blood transfusion perioperatively. At operation the pericardium was found to be very thickened with haemorrhagic pericarditis, clots, and fibrin in the pericardial sac. A 4 × 5 cm window was created. Appreciable pericardial fluid was not found at operation although 800 ml was subsequently evacuated through surgical drains, possibly from a loculated collection. A further operation was required a few days later at which formal pericardiectomy and removal of a clot from the left pleural cavity was undertaken.

The patient did well after operation and was discharged home.

Histology of the pericardium showed fibrinous haemorrhagic pericarditis. Histology of a lung biopsy taken at the time of the first operation showed scattered inflammatory cells (mainly lymphohistiocytic with a few polymorphs). There was no evidence of granulomata or vasculitis in either tissue.

Discussion

Wegener's granulomatosis is an uncommon vasculitis that forms part of the spectrum of diseases including polyarteritis nodosa and temporal arteritis. First described in 1931 by Klinger[3] and further characterised by Wegener in 1936,[4] there have since been many further reports and series. A serological marker useful in confirming the diagnosis and monitoring disease activity have become available (the c-ANCA test),[5–8] and effective treatment in the form of cytotoxic drugs and corticosteroids is now available. Remission and long-term survival are now possible.[1]

The characteristic features of generalised Wegener's granulomatosis are involvement of the upper and lower respiratory tract and kidneys. More limited forms are recognised in which there may be involvement of only the upper airways without major involvement of the lungs or kidneys.

Implication of other organ systems is, however, common; the table shows two series reporting the frequency with which other systems are involved. The difference in frequencies is likely to reflect the fact that in the series of Pinching *et al* all the cases were referred due to renal failure and were also severe and advanced.[2] The series of Hoffman *et al* is the largest available (24 year follow up of 158 patients) and includes less severely affected cases and many that were treated

Table Frequency (%) of organ system involvement in Wegener's granulomatosis from two published series

Organ system	*Hoffman et al*[1]	*Pinching et al*[2]
Kidney	72	100
Lung	85	100
Ear, nose, and throat	92	94
Systemic features (malaise fever and weight loss)	50	94
Liver	—	89
Musculoskeletal	67	—
Muscle	—	83
Joints	—	78
Eye	52	78
Peripheral nervous system	15	67
Skin	45	67
Heart	6	44
Central nervous system	8	44

early and had long survival times.[1] Fauci and Wolf have also reported cardiac involvement in 30% of cases of Wegener's granulomatosis examined at necropsy.[9]

Cardiac involvement seems to occur in 6% to 44% of cases, the higher figure being associated with more severe disease and with a higher rate of postmortem examination. Cases of Wegener's granulomatosis in publications before 1980 that recorded cardiac involvement were collated and reviewed by Forstot *et al.*[10] On the basis of pathological examination the following frequency of features was described (the percentage is of cases with cardiac involvement): coronary arteritis in 50% of cases, pericarditis in 50%, myocarditis in 25%, valvulitis or endocarditis in 21% (all of these being of the mitral or tricuspid valve), conduction system granulomata in 17%, arteritis of the blood supply to the sinus node in 13%, arteritis of blood supply to the atrioventricular node in 13%, myocardial infarction in 11%, and epicarditis in 8%. These figures probably overestimate the incidence of extensive disease as they were collated before c-ANCA measurements were introduced.

There have been several published reports of Wegener's granulomatosis with cardiac involvement since 1980.[1 2 11–22] Many of these reports are clinical rather than pathological descriptions, as with improved diagnosis and treatment most patients now survive. Heart muscle disease,[20 21] varying degrees of heart block and supraventricular tachycardia,[2 12 13 14] and previously unreported presentations of cardiac mass,[22] pericardial tamponade,[12 15] aortic valvulitis,[16 17] and constrictive pericarditis[12] have been described.

We think that the cardiac conditions in the patients we describe were directly attributable to Wegener's granulomatosis. Although histology failed to show characteristic features, all three cases were deliberately operated on at a time of good disease control. In case 1 the nature of the histology of the valve is not typical of chronic rheumatic valve disease and is likely to represent the sequelae of a valvulitis quiescence as a result of treatment. The prolongation of the PR interval seen in this young patient may also reflect involvement of the heart by Wegener's granulomatosis, either by arteritis affecting the blood supply to the conducting tissue or by direct granulomatous involvement of the conducting system. In the second and third cases, although histological proof in the form of vasculitis or granulomata is again lacking, the temporal relation of the condition to the active Wegener's granulomatosis is striking. In the third case the patient had been undergoing stable regular haemodialysis for five months. Pericardial involvement was not present when her renal function was declining and severe (preceding her relapse with life threatening lung haemorrhage). The development of pericarditis after that relapse at a time when her uraemia was stable and well controlled by dialysis makes the likelihood of uraemia as a cause for her pericardial disease, although a possibility, much less likely.

Pathologically confirmed aortic valvulitis has, to our knowledge, been recorded as a complication of Wegener's granulomatosis on only two previous occasions. In the first of these, characteristic pathological features were described post mortem, with granulomata and arteritis affecting the valve and aortic root.[16] In the second, aortic valve replacement was required and histology, as in our case 1, showed non-specific features compatible with the diagnosis.[17] Clinical abnormalities of the aortic valve in association with Wegener's granulomatosis have been described on two other occasions.[18 19] The clinical syndrome of constrictive pericarditis in association with Wegener's granulomatosis has been recorded on only one previous occasion and that was in conjunction with uraemia (as in our third case) and followed intervention for an episode of pericardial tamponade.[12] Pericardial surgery was required on that occasion and this has also been described for another case of pericardial tamponade associated with Wegener's granulomatosis.[15]

In summary, Wegener's granulomatosis not infrequently affects the heart, particularly in more advanced cases of the disease, and may cause clinically important complications. Pathologically, pericarditis and coronary arteritis are the commonest manifestations. Clinically, evidence of pericarditis and its complications as well as supraventricular arrhythmias and varying degrees of heart block are the most common features. The advent of c-ANCA monitoring and the benefits of modern therapeutic approaches have resulted in many long-term survivors with previously severe Wegener's granulomatosis. Such patients not infrequently relapse with atypical presentations and cardiac involvement may therefore be seen more often in the future.

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